

Langevin Stabilization of Molecular Dynamics

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(October 7, 2000)*

This paper shows the possibility of using very mild stochastic damping to stabilize long time step integrators for Newtonian molecular dynamics. More specifically, stable and accurate integrations are obtained for damping coefficients that are only a few percent of the natural decay rate of processes of interest, such as the velocity autocorrelation function. Two new multiple time stepping integrators, Langevin Molly (LM) and Brünger-Brooks-Karplus-Molly (BBK-M), are introduced in this paper. Both use the mollified impulse method for the Newtonian term. LM uses a discretization of the Langevin equation that is exact for constant force, and BBK-M uses the popular Brünger-Brooks-Karplus integrator (BBK). These integrators, along with a nonsymplectic, stochastic, and extrapolative method (termed LN by its authors), are evaluated across a wide range of damping coefficient values. Using LM and mild damping of 0.2 ps^{-1} long time steps of 14 fs are possible in simulations containing explicitly modeled flexible water. With BBK-M and the same damping coefficient time steps of 12 fs are possible for the same system. Similar results are obtained for a solvated protein-DNA simulation of estrogen receptor ER with estrogen response element ERE. A parallel version of BBK-M runs nearly 3 times faster than the reversible reference system propagator algorithm (r-RESPA or Verlet-I) when using the largest stable time step on each one, and it also parallelizes well. When using mild damping, LM is superior to the other methods because it is symplectic in the zero damping limit, and because it uses a discretization of the Langevin equation that is exact for constant force. The computation of diffusion coefficients for flexible water and ER/ERE shows that when mild damping of up to 0.2 ps^{-1} is used the dynamics are not significantly distorted. When larger damping coefficients are used, as one would for the implicit modeling of solvent molecules, the method LN is superior, with LM closely following.

I. INTRODUCTION

The length of (Newtonian) molecular dynamics (MD) simulations is limited by the length of the time steps that can be used. A moderate increase is possible using the reversible reference system propagator algorithm (r-RESPA or Verlet-I) multiple time stepping (MTS) method,^{1,2} and a further 50% increase can be attained with the mollified impulse method (MOLLY).³ However, the fairly long time steps that would be justified by accuracy considerations alone are not possible due to numerical instability.^{4,5} On the other hand for Langevin dynamics, the application of an appropriate MTS method, namely a nonsymplectic, stochastic, and extrapolative method termed LN by its authors⁶, permits time steps to be chosen on the basis only of accuracy considerations and reproduces many properties of Newtonian dynamics. This paper shows for Newtonian molecular dynamics the possibility of using very mild stochastic damping to stabilize an MTS integrator for long time steps. More specifically, stable and accurate integrations are obtained for damping coefficients that are only a few percent of the natural decay rate of processes of interest, such as the velocity autocorrelation function.

Two new MTS integrators, Langevin Molly (LM) and Brünger-Brooks-Karplus-Molly (BBK-M), are introduced in this paper. Both use the mollified impulse method for the Newtonian term. LM uses a discretization of the Langevin equation that is exact for constant force, and BBK-M uses the popular Brünger-Brooks-Karplus integrator (BBK). These integrators, along with LN, are evaluated across a wide range of damping coefficient or collision frequency values. Using LM and mild damping of 0.2 ps^{-1} long time steps of 14 fs are possible in simulations containing explicitly modeled flexible water. With BBK-M and the same damping coefficient time steps of 12 fs are possible for the same system. Similar results are obtained for a solvated protein-DNA simulation of estrogen receptor ER with estrogen response element ERE. When using mild damping, LM is superior to the other methods because it is symplectic in the zero damping limit, and because it uses a discretization of the Langevin equation that is exact for constant force. The computation of diffusion coefficients for flexible water and ER/ERE shows that when collision frequencies of up to 0.2 ps^{-1} are used the dynamics are not significantly distorted. When larger damping coefficients are used, as one would for the implicit modeling of solvent molecules, the method LN is superior, with LM closely following.

The paper is organized as follows: Section II motivates the mollified impulse method, the integrator used for the Newtonian term of the equation, and the use of Langevin dynamics for stabilization of the integrator in constant temperature dynamics. Section III compares single time stepping integrators for the Langevin term. Section IV introduces the MTS integrators for Langevin dynamics and Langevin stabilization, including BBK-M, LM, and LN. Section V presents an evaluation of the new integrators along with LN. Finally, Section VI presents the conclusions.

II. MOTIVATION

Molecular dynamics for a classical unconstrained simulation requires the solution of Newton's equations of motion:

$$\mathbf{M} \frac{d^2}{dt^2} X(t) = -\nabla U(X(t)) \quad (1)$$

where \mathbf{M} is a diagonal matrix of atomic masses, $X(t)$ is the collective atomic position vector, U is the potential energy, typically given by

$$U = U^{\text{bonded}} + U^{\text{nonbonded}}, \quad (2)$$

$$U^{\text{bonded}} = U^{\text{bond}} + U^{\text{angle}} + U^{\text{dihedral}} + U^{\text{improper}}, \quad (3)$$

$$U^{\text{nonbonded}} = U^{\text{Lennard-Jones}} + U^{\text{electrostatic}}, \quad (4)$$

and the gradient vector $-\nabla U(X(t))$ is the force.

The Verlet-I/r-RESPA MTS impulse method splits the force into different components whose dynamics correspond to different time scales, which are then represented as appropriately weighted impulses, with weights determined by consistency. Henceforward the time dependence will not be included in the position or velocity vector. The impulse method for two different time steps is

$$\mathbf{M} \frac{d^2}{dt^2} X = - \sum_{n'=-\infty}^{\infty} \delta t \delta(t - n' \Delta t) \nabla U^{\text{fast}}(X) - \sum_{n=-\infty}^{\infty} \Delta t \delta(t - n \Delta t) \nabla U^{\text{slow}}(X) \quad (5)$$

where δ is the Dirac impulse function, and the partitioning of U into U^{fast} and U^{slow} is chosen so that an appropriate time step Δt for the slow part of the force is larger than a time step δt for the fast part.

Verlet-I/r-RESPA was proposed but not implemented by the authors of Refs. 1 and 7 and independently discovered by the authors of Ref. 2, who also demonstrated its usefulness. It permits an increase to 4 fs in the length of the longest time step Δt . When the method was introduced, it was predicted that there would occur resonances that might induce instability if the frequency of the slow force impulse coincides with a normal mode frequency of the system.^{1,8} Resonance produces an oscillation in the positions whose amplitude increases with time. More surprisingly, there is also a problem for long time steps just smaller than half the period of the fastest normal mode.^{4,9} There is also empirical evidence that time steps of 5 fs or greater are not possible with this method.¹⁰

A. MOLLY: The mollified impulse method

MOLLY is a family of integrators⁴ that counteracts the instabilities present in the MTS Verlet-I/r-RESPA integrator. This is accomplished by perturbing the potential using time averaged positions. The time average is obtained by doing dynamics over vibrations using forces that produce those vibrations. Thus,

$$U^{\text{slow}}(X) \rightarrow U^{\text{slow}}(\mathcal{A}(X)), \quad (6)$$

with the force defined as a gradient of this averaged potential,

$$-\nabla U^{\text{slow}}(X) \rightarrow -\mathcal{A}_{\mathbf{X}}(X)^T \nabla U^{\text{slow}}(\mathcal{A}(X)), \quad (7)$$

where $\mathcal{A}_{\mathbf{X}}(X)$ is a matrix.

This perturbation is supposed to compensate for finite Δt artifacts. Intuitively, averaged positions are better than instantaneous values for a rapidly changing trajectory $X(t)$. Perturbing the potential rather than the force ensures that the numerical integrator remains symplectic.¹¹ The force used by MOLLY is the gradient of the perturbed potential.³ MOLLY can be seen as a filter that eliminates components of the slow force impulse in the directions of the fast forces, and thus improves the stability of Verlet-I/r-RESPA. Different averaging functions give rise to MOLLY integrators with different stability and accuracy properties. Here we present a time averaging that completely eliminates the components of $-\nabla U^{\text{slow}}$ in the directions of the fast forces. A more complete statement is found on Appendix A. Our starting point is the backward Euler averaging:

$$\mathcal{A}(X) = X - \tau^2 \mathbf{M}^{-1} \nabla U^{\text{fast}}(\mathcal{A}(X)), \quad (8)$$

where τ is a parameter with units of time. This averaging is obtained with one step of backward Euler starting with zero velocities. Backward Euler is chosen because of its stable behavior in the limit $\tau \rightarrow \infty$.

Assume that $U^{\text{fast}}(X)$ can be written as $U^{\text{fast}}(X) = \chi(g(X))$, where $g(X)$ is a vector of independent length constraint functions. The elements of $g(X)$ are of the form

$$g^k(X) = X^T \mathbf{G}_k X - l_k^2 \quad (9)$$

where the \mathbf{G}_k are symmetric matrices and l_k are rest lengths. Thus, for example,

$$U_k^{\text{bond}}(X) = \frac{1}{2} K_B \left(\sqrt{g^k(X) + l_k^2} - l_k \right)^2,$$

where K_B is a bond-force constant and l_k is a reference bond length. Similar formulations exist for the bond angle energy employing the law of cosines in a triangle. Allowing $\tau \rightarrow \infty$ gives the equations for $\mathcal{A}(X)$ and μ

$$\begin{cases} \mathbf{M}(\mathcal{A}(X) - X) + g_X^T(\mathcal{A}(X))\mu = 0, \\ g(\mathcal{A}(X)) = 0, \end{cases} \quad (10)$$

which are termed *Equilibrium**; this method completely eliminates components of $-\nabla U^{\text{slow}}$ in the directions of the constraints g_X^T . Appendix A contains a proof of this statement, as does Ref. 12, and the main result is summarized here: Let U_{xx} be a Hessian matrix obtained from the potential energy U , and $\rho(A)$ represent the spectral radius of a matrix A . Then, the stability condition for *Equilibrium** MOLLY on the longest time step ($\Delta t \rho(M^{-1/2} U_{xx}^{\text{slow}} M^{-1/2})^{1/2} < 2$) is less restrictive than that of the popular leapfrog integrator ($\Delta t \rho(M^{-1/2} U_{xx} M^{-1/2})^{1/2} < 2$), because it is limited by the fastest frequencies in the slow forces ($-\nabla U^{\text{slow}}$) rather than by the overall fastest frequencies (in $-\nabla U^{\text{fast}}$). Thus, it allows one to choose the long time steps independently of the short time steps. An earlier version of this averaging, called *Equilibrium*, is in Ref. 13. This paper presents a technique to further stabilize MTS by adding a mild Langevin damping term. We start by providing a review of Langevin dynamics.

Finally, we illustrate the effect of applying *Equilibrium** to a simple model problem. Consider a system of three charged particles and one spring in 1-D as illustrated in Fig. 1. This system has a potential energy given by

$$U(x) = \overbrace{\frac{1}{2}k(x_1 - x_2 - l)^2}^{U^{\text{fast}}(x)} - \underbrace{(x_3 - x_2)^{-1} + (x_3 - x_1)^{-1}}_{U^{\text{slow}}(x)}, \quad (11)$$

which can be split into fast and slow components as highlighted above.

The *Equilibrium** MOLLY method defines a perturbed potential

$$\hat{U}(x) = U^{\text{fast}}(x) + U^{\text{slow}}(\mathcal{A}(x)), \quad (12)$$

where $\mathcal{A}(x)$ is found from Eq. (10). Let $\mathcal{A} = [\bar{x}_1, \bar{x}_2, \bar{x}_3]$; then $g(\mathcal{A}(x))$ is the vector of constraints with $g_1(\mathcal{A}(x)) = (\bar{x}_2 - \bar{x}_1)^2 - l^2$, $g_2(\mathcal{A}(x)) = (\bar{x}_2 - \bar{x}_1)^2 - l^2$, and $g_3(\mathcal{A}(x)) = 0$. The averaged positions and the MOLLY filter matrix are given by

$$\mathcal{A}(x) = \begin{bmatrix} (x_1 + x_2 - l)/2 \\ (x_1 + x_2 + l)/2 \\ x_3 \end{bmatrix}, \quad \mathcal{A}_x(x) = \begin{bmatrix} 1/2 & 1/2 & 0 \\ 1/2 & 1/2 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

The result of applying the MOLLY filter to the slow force,

$$U^{\text{slow}}(x) \longrightarrow U^{\text{slow}}(\mathcal{A}(x)), \quad (13)$$

$$F^{\text{slow}}(x) \longrightarrow \mathcal{A}_x(x)^T [F_1^{\text{slow}}(\mathcal{A}(x)), F_2^{\text{slow}}(\mathcal{A}(x)), F_3^{\text{slow}}(\mathcal{A}(x))]^T, \quad (14)$$

is to add equal forces to each atom at either end of the spring, thus not causing any stretching of the spring. Only a translation of the spring system is produced. Thus, no possibility of instability due to the slow force impulse is introduced.

B. Regular Langevin Dynamics

Regular Langevin dynamics models the effect of molecules not explicitly included in the simulation, such as solvent molecules^{14,15} and molecules outside the boundary of the computational domain. The effect of the missing molecules on the dynamics of the solute macromolecule is incorporated by an electrostatics *potential-of-mean-force term* added to $U(X)$, by *random collisions* (the random force vector below), and by a *frictional drag on its motion through the solvent* (the friction term $-\gamma M \dot{X}$ below). This behavior can be produced by a system of stochastic differential equations given by

$$M d\dot{X} = -\nabla U(X) dt - \gamma M \dot{X} dt + \sqrt{2\gamma k_B T} M^{1/2} dW(t), \quad (15)$$

where X is the position, \dot{X} is the velocity, γ is the collision frequency, $W(t)$ is a vector of independent standard Wiener processes (Ref. 16, p. 28), k_B is the Boltzmann constant, and T is the Langevin bath temperature. These equations correspond to a constant temperature ensemble.

In the classical solvent modeling application of the Langevin Eq. (15) the frictional term is assumed to be proportional to the velocity of the system. The constant of proportionality or friction coefficient is given by $\gamma * \text{mass}$. It is useful to define $2/\gamma$ as the velocity relaxation time: this is the time it takes for higher frequency motion to be damped by a factor of $1/e$. A typical value used for water as a solvent is suggested in Ref. 17 to be $\gamma = 50 \text{ ps}^{-1}$.

C. Effect of Damping on the Dynamics

Too large γ overdamps the low-frequency vibrational modes. For example, spectral densities appear smoother, and so does the decay of various correlations functions.¹⁵ However, it has been reported that the dynamics are preserved by stochastic methods as long as the collision frequencies are small enough. For example, Ref. 18 reports quantitatively correct diffusion coefficients for argon. More recently, Refs. 15 and 19 use a γ of $5\text{--}20 \text{ ps}^{-1}$ to stabilize MTS for the protein BPTI. Plots of various spectral properties seem to indicate that several dynamical properties are preserved. However, diffusion coefficients are not computed. Furthermore, it is not clear whether such results extend to solvated systems. On the one hand, for fluids, the addition of even a mild Langevin term may cause undue damping, since the velocity autocorrelation function decays much more slowly, as $t^{-3/2}$ for 3-D liquids, see Ref. 20, p. 310. On the other hand, for simulations of biological systems this long tail effect should not be important.

D. Langevin Stabilization

This work explores *Langevin stabilization*, the use of mild damping to stabilize otherwise unstable integrators without distorting the dynamics. In the limit of $\gamma = 0$, Newtonian mechanics would be recovered if it were not for the temperature control mechanism of Langevin dynamics. Thus, any instabilities of the underlying MTS integrator will become apparent as γ approaches zero. A prescription for estimating the appropriate values of γ is to choose $2/\gamma$ much larger than the relaxation times of processes of interest, such as the velocity autocorrelation function. Then, computation of dynamical quantities like the diffusion coefficient serves to validate the proposed value of γ .

Once the largest possible γ that does not distort the dynamics has been fixed, the largest time step can be determined. Numerical stability establishes the limit of the largest time step that can be taken. The protocol just described is used to determine appropriate values of γ and Δt for several MTS integrators applied to flexible water and solvated biomolecule systems. See Section 5.1.

The method as presented here does not yield a constant energy simulation but rather a constant temperature sampling. However, it should give a physically reasonable simulation in the context of stochastic boundary conditions.^{21–24} It would be interesting to compare the relative merits of LM against extended Hamiltonian methods such as Nosé-Hoover dynamics^{25–27} and possibly to combine them.

III. SINGLE TIME STEPPING INTEGRATORS FOR LANGEVIN DYNAMICS

After having considered the integrators for Newtonian dynamics and motivated the use of damping to stabilize them, a description of the integrators for the Langevin term follows. As a starting point, Eq. (15) is simplified and rewritten as a system of two coupled first order differential equations:

$$dX = V dt, \quad dV = -\mathbf{M}^{-1} \nabla U(X) dt - \gamma V dt + \sqrt{2\gamma k_B T} \mathbf{M}^{-1/2} dW(t) \quad (16)$$

where $V(t) := \dot{X}(t)$ is the velocity.

Different discretizations of Eq. (16) are available in the literature, but one of the most popular is the **BBK** integrator:²⁸

half a kick:

$$V^{n+1/2} = (1 - \frac{1}{2}\gamma\Delta t)V^n + \frac{1}{2}\Delta t\mathbf{M}^{-1}(-\nabla U(X^n) + R^n). \quad (17)$$

drift:

$$X^{n+1} = X^n + \Delta t V^{n+1/2}. \quad (18)$$

half a kick:

$$V^{n+1} = \frac{V^{n+1/2} + \frac{1}{2}\Delta t\mathbf{M}^{-1}(-\nabla U(X^{n+1}) + R^{n+1})}{1 + \frac{1}{2}\gamma\Delta t}, \quad (19)$$

where

$$R^n = \sqrt{\frac{2\gamma k_B T}{\Delta t}} \mathbf{M}^{1/2} Z^n, \quad (20)$$

and Z^n represents a vector of independent Gaussian random numbers of mean zero and variance one. The symbols V^n and V^{n+1} represent the velocities just before the n th kick and after the $(n+1)$ st kick; X^n and X^{n+1} are the positions before and after the n th drift. $V^{n+1/2}$ is a temporary vector of velocities after the n th kick.

It is reasonable to expect an integrator for Langevin dynamics be exact for constant force; **Langevin impulse**, one such single time stepping scheme, is proposed in Ref. 19. This method was implemented and analyzed by one of the authors in Ref. 12. Another example of such a method is the one proposed in Ref. 29. Langevin impulse is based on the idea of splitting, and it samples from a *bivariate* Gaussian distribution. The Langevin impulse discretization of Eq. (16) consists of half a kick, a “fluctuation,” followed by another half a kick. The method is

half a kick:

$$V^{n+\epsilon} = V^n - \frac{1}{2}\Delta t\mathbf{M}^{-1}\nabla U(X^n). \quad (21)$$

fluctuation:

$$V^{n+1-\epsilon} = \exp(-\gamma\Delta t)V^{n+\epsilon} + \sqrt{2\gamma k_B T} \mathbf{M}^{-1/2} R_1^{n+1}, \quad (22)$$

$$X^{n+1} = X^n + \Delta t \frac{1 - \exp(-\gamma\Delta t)}{\gamma\Delta t} V^{n+\epsilon} + \sqrt{2\gamma k_B T} \frac{\mathbf{M}^{-1/2}}{\gamma} R_2^{n+1}. \quad (23)$$

half a kick:

$$V^{n+1} = V^{n+1-\epsilon} - \frac{1}{2}\Delta t \mathbf{M}^{-1} \nabla U(X^{n+1}), \quad (24)$$

where

$$R_1^{n+1} = \int_{t^n}^{t^{n+1}} \exp(-\gamma(t^{n+1} - t)) dW(t), \quad R_2^{n+1} = \int_{t^n}^{t^{n+1}} (1 - \exp(-\gamma(t^{n+1} - t))) dW(t); \quad (25)$$

$t^{n+1} = t^n + \Delta t$; $V^{n+\epsilon}$ and $V^{n+1-\epsilon}$ represent temporary velocities between the n st and $(n+1)$ st kick; and R_1^{n+1} and R_2^{n+1} are joint Gaussian random variables of zero mean and some covariance matrix C . The procedure for generating these random variables is summarized in Appendix B. These integrators are combined with MTS integrators for Newtonian dynamics in the next section.

IV. MTS INTEGRATORS FOR LANGEVIN DYNAMICS

The combination of single time stepping integrators for the Langevin term with MTS integrators for the Newtonian term of Eq. (16) produces MTS integrators for Langevin dynamics. The integrators that were implemented and tested for this paper are described next. The first three use symplectic MTS integrators for the Newtonian term. The last one uses an extrapolative (and non-symplectic) MTS integrator for the Newtonian term. It is shown that with mild damping, symplectic integrators behave better than non-symplectic ones. However, for relatively large damping, there is no apparent advantage of using a symplectic integrator for the Newtonian part.

A. BBK-I

BBK-I is the combination of the Verlet-I/r-RESPA method with BBK. The only difference with the impulse method is that in the innermost loop BBK is substituted for the Verlet/leapfrog method.

B. BBK-M

BBK-M is the combination of the *Equilibrium** MOLLY method with BBK. Like BBK-I, the only change is the use of BBK in the innermost integration step.

C. LM

LM is a combination of the *Equilibrium** MOLLY method with Langevin impulse. Again, the only change is that in the innermost loop Langevin impulse is substituted for the Verlet/leapfrog method.

D. LN: An extrapolative MTS integrator for Langevin dynamics

LN is a method introduced in Refs. 9 and 15. It is a triple time stepping method that combines constant extrapolation (CE) on the outer time step, midpoint extrapolation (ME) on the medium time step, and midpoint BBK on the innermost time step. This particular formulation is that of Ref. 6. The motivation of LN is to avoid the instability due to the impulsive nature of Verlet-I/r-RESPA by using extrapolative methods. CE and ME used in a linear problem are unstable even for a scalar problem; however, for a linear problem the magnitude of the eigenvalues of the propagation matrix is bounded independently of the long time step Δt . For CE and ME to be stable, a moderate

amount of damping is needed. The instability of ME at small outer time steps is milder than that of CE, even though it is not bounded. These results motivate the choice of integrators for the different force components in LN: The slow forces with longest time step are integrated using CE; whereas the medium forces are integrated with ME.

Assume that the medium time step $\Delta t_m = k_1 \delta t$ and the longest time step $\Delta t = k_2 \Delta t_m$, where k_1 and k_2 are integers. Then, given positions X and velocities V , one long step of LN consists of

slow force evaluation:

$$F^{\text{slow}} := -\nabla U^{\text{slow}}(X), \quad (26)$$

followed by k_2 steps of {

medium force evaluation:

$$F^{\text{med}} := -\nabla U^{\text{med}}(X + \frac{1}{2} \Delta t_m V), \quad (27)$$

followed by k_1 steps of {

half a drift:

$$X := X + \frac{1}{2} \delta t V, \quad (28)$$

kick:

$$F^{\text{fast}} := -\nabla U^{\text{fast}}(X), \quad F^{\text{rand}} := \sqrt{\frac{2\gamma k_B T}{\delta t}} \mathbf{M}^{1/2} Z^n, \quad (29)$$

$$V := \frac{V + \frac{1}{2} \delta t \mathbf{M}^{-1} (F^{\text{slow}} + F^{\text{med}} + F^{\text{fast}} + F^{\text{rand}})}{1 + \gamma \delta t}, \quad (30)$$

half a drift:

$$X := X + \frac{1}{2} \delta t V. \quad (31)$$

}
}

V. NUMERICAL EVALUATION OF LANGEVIN DYNAMICS INTEGRATORS

Results of numerical evaluation of the 4 integrators for Langevin dynamics described above are reported here. Most experiments were performed using *flexible water*; that is, vibrations of bonds and angles are included in the TIP3P water model.³⁰ The potential energy of flexible water is given by

$$U^{\text{electrostatic}} = C \frac{q_i q_j}{x_{ij}}, \quad (32)$$

$$U^{\text{Lennard-Jones}} = 4\epsilon_{ij} \left(\left(\frac{\sigma_{ij}}{x_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{x_{ij}} \right)^6 \right) SW(x_{ij}), \quad (33)$$

$$U^{\text{bond}} = K_B (x_{ij} - l_{ij})^2, \quad (34)$$

$$U^{\text{angle}} = K_A (\theta - \theta_0)^2. \quad (35)$$

where $x_{ij} = \|\vec{\mathbf{x}}_j - \vec{\mathbf{x}}_i\|$. For our discussion these potentials are split as follows:

$$U^{\text{fast}} = U^{\text{fast,bonded}} + U^{\text{fast,nonbonded}}, \quad (36)$$

$$U^{\text{fast,bonded}} = U^{\text{angle}} + U^{\text{bond}}, \quad (37)$$

$$U^{\text{fast,nonbonded}} = U^{\text{fast,elect}} + U^{\text{Lennard-Jones}}, \quad (38)$$

$$U^{\text{fast,electrostatic}} = U^{\text{electrostatic}} SW(x_{ij}), \quad (39)$$

$$U^{\text{slow}} = U^{\text{electrostatic}} - U^{\text{fast,electrostatic}}. \quad (40)$$

The switching function $SW(x_{ij})$ serves to split the electrostatic potential into slow and fast parts (and also to bring the Lennard–Jones force to zero smoothly) so that the force is a derivative of the potential even when using cutoff.³¹ It is defined by

$$SW(x_{ij}) = \begin{cases} 0 & \text{if } x_{ij} > \text{cutoff}, \\ 1 & \text{if } x_{ij} \leq SWon, \\ \frac{(\text{cutoff}^2 - x_{ij}^2)(\text{cutoff}^2 + 2x_{ij}^2 - 3SWon^2)}{(\text{cutoff}^2 - SWon^2)^2} & \text{if } SWon \leq x_{ij} < \text{cutoff}. \end{cases}$$

For flexible water, $C = 332.0636$ (kcal/mol)K⁻¹, $K_A = 55$ (kcal/mol)degrees², $K_B = 450$ (kcal/mol)Å², $q_O = 0.417$ e, $q_H = -0.834$ e, $l_{OH} = 0.957$ Å, $l_{H-H} = 1.514$ Å, $\theta_0 = 104.52$ degrees. The Lennard–Jones parameters are $\sigma_{H-H} = 0.4$ Å, $\sigma_{O-H} = 1.75253$ Å, $\epsilon_{H-H} = 0.046$ kcal/mol, $\epsilon_{O-H} = 0.08365$ kcal/mol.

Earlier experiments suggest that flexible water models are particularly sensitive to destabilizing artifacts in numerical integrators.¹⁰ The successful use of time steps of 6 fs using *Equilibrium** MOLLY is reported in Ref. 3.

The criterion used to measure accuracy is to consider the worse of the errors in average total energy and temperature. In particular, the deviation from the “correct” average energy is computed by comparing against a trajectory with $\Delta t = 1$ fs for a given γ . An error of at most 3% is considered accurate. Similarly, the error of the average simulated temperature with respect to the Langevin temperature was computed. In general, the error in the energy is observed to be a stricter measure of accuracy than is the error in the temperature.

Finally, to show that with the proposed value of γ one obtains the correct dynamics, we also obtained the mean square displacement $R(\tau)$ (MSD) as a function of time and the self-diffusion coefficient D using Einstein’s relation $3D \sim R(\tau)/(2\tau)$. The procedure to compute these quantities is described in more detail in Refs. 14 and 32, among others. The self-diffusion coefficient was computed by averaging over all molecules and all time origins of 250 ps simulations of a 10 Å radius sphere of water with 141 molecules.

To get the diffusion coefficient for liquid water one would normally use periodic boundary conditions to avoid surface tension effects. The program “Not Another Molecular Dynamics program” (NAMD) version 1.5 in which we tested our methods does not implement periodic boundary conditions with an Ewald sum, although it is implemented in NAMD 2.1.³³ Hence, we have used spherical constraints with a radius of 11 Å. The quantities we compute are not physically correct but they are of the same nature as the physical quantities and should serve well to compare the proposed methods to the leapfrog method, which is of known quality. The protein–DNA simulation of the estrogen receptor ER and part of the DNA of an estrogen response element ERE³⁴ was solvated in a 35 Å radius sphere of flexible water with 17527 atoms. It was tested using BBK-M in NAMD 2.1. Periodic boundary conditions in all directions were used, and the periodic box enclosed the whole system. The topology parameters were those of CHARMM 22 for proteins^{35,36} and nucleic acids;³⁷ parameters for a zinc patch for DNA were from Ref. 38.

A. Results with Langevin stabilization

Accuracy results for Langevin stabilization of flexible water are summarized in the first numerical row of Tables I and II. Note that BBK-I and LN are not suitable methods for Langevin stabilization. On the other hand, Langevin stabilization of MOLLY is very successful: using LM long time steps of 14 fs are possible for moderate accuracy, and long time steps of 10 fs for higher accuracy; both sets of result use a $\gamma = 0.2$ ps⁻¹. LM is more accurate and able to take longer time steps Δt than BBK-M in all cases. Our tests of LN combine medium and fast forces; LN does not produce satisfactory results for Langevin stabilization, since the underlying extrapolative nonsymplectic integrator is unstable even for linear problems, which can only be overcome with a relatively large damping γ of 20 ps⁻¹ or greater.

Table III shows that for flexible water with a $\gamma = 0.2$ ps⁻¹ for all stable time steps, for both LM and BBK-M, the diffusion coefficients are correct, compared to those of leapfrog and *Equilibrium** MOLLY with a time step of 1 fs. Table IV shows similar, albeit less extensive, results for the solvated ER/ERE system.

B. Results with Langevin dynamics

The results for regular Langevin dynamics are summarized in the last 5 rows of Tables I and II. LM is successful here also: with $\gamma = 50$ ps⁻¹, time steps as large as 35 fs are possible. This is superior to BBK-I or BBK-M, for which the maximum time step is 16 fs. In general, LM allows greater γ and Δt to be taken than BBK-I and BBK-M. For example, time steps of 50 fs can be taken with $\gamma = 100$ ps⁻¹ using LM. A summary of the results appear in Fig. 2. For the modeling of an implicit solvent, LM is inferior to LN. The latter allows long time steps of 50 fs for the same

levels of accuracy with $\gamma = 50 \text{ ps}^{-1}$. These results are consistent with Ref. 15, which reports long time steps using LN of 12 fs for flexible water, 48 fs for a biomolecule in water, and 96 fs for a biomolecule in vacuum.

C. Implementation and Performance

All the methods described here are implemented in a testing program called PROTOmol.³⁹ The performance of *Equilibrium* MOLLY, with and without langevin damping, was evaluated using the parallel molecular dynamics program NAMD 2.1. The test problem was the protein-DNA simulation of ER/ERE described above. Timings are shown in Table V, and method speedups are shown in Table VI.

Parallelism is achieved by doing a spatial decomposition of the system into boxes called “patches” with the constraint that each H group is kept in a single patch. An H group is a heavy atom and all hydrogens covalently bonded to it. A patch resides completely in one processor. *Equilibrium* parallelizes well, since the averaging is performed on each H group independently of all other H groups, i.e., H groups decouple for the averaging: All the information needed to do the averaging and mollification, that is, computing $\mathcal{A}(X)$ and $-\mathcal{A}_{\mathbf{X}}(X)^T \nabla U^{\text{slow}}$, is local to the patch; thus, there is no extra communication requirement. There is, however, an extra memory requirement needed to store the averaged positions. The filter matrices $\mathcal{A}_{\mathbf{X}}(X)^T$ are not formed completely, but rather the matrix–vector product $-\mathcal{A}_{\mathbf{X}}(X)^T \nabla U^{\text{slow}}$ is computed from X and $\mathcal{A}(X)$. An efficient computation of $\mathcal{A}_{\mathbf{X}}(X)^T$ for *Equilibrium** is presented in Ref. 12. It makes use of the special structure of this matrix.

VI. CONCLUSIONS

This paper has shown that it is possible to stabilize symplectic integrators for molecular dynamics using very mild damping that is less than the decay rate of the velocity autocorrelation function. This was illustrated by introducing LM: it combines the *Equilibrium** mollified impulse method, which extends the stability of the Verlet-I/r-RESPA impulse method, and a Langevin impulse method, which is exact for constant forces. BBK-M, a close variant of LM, can take long time steps of 14 fs with a γ of 0.2 ps^{-1} . BBK-M has been implemented and tested with biomolecules in explicit flexible solvent in the parallel molecular dynamics program NAMD 2.1. It is 3 times faster than Verlet-I/r-RESPA on a protein-DNA simulation. It is possible that combining even stabler MOLLY methods with mild damping, one may achieve time steps for molecular dynamics that are only limited by accuracy, rather than stability. Also, our computation of diffusion coefficients suggests that Langevin stabilization is applicable to solvated biomolecular systems: this is supported by preliminary results on a solvated protein-DNA simulation of the estrogen receptor ER and the DNA of the estrogen response element ERE. Nevertheless, more extensive study and consideration of this question would more clearly specify the limitations and applicability of the methods presented here: for constant temperature simulations, in the presence of stochastic boundary conditions, and as an alternative to (and possibly combined with) extended Hamiltonian methods such as Nosé-Hoover.

ACKNOWLEDGMENTS

We are grateful to Jim Phillips for assisting us in the implementation of *Equilibrium* into NAMD 2.1. We are also thankful to Dr. Atul Bahel for helping us to compute the diffusion coefficients, and reading a version of this manuscript. Mr. Marc Ma contributed one of the figures. This work was supported in part by NSF Grants DMS-9971830, DBI-9974555 and NIH Grant P41RR05969, and by the Department of Computer Science and Engineering at the University of Notre Dame, IN.

APPENDIX A: LINEAR STABILITY OF *EQUILIBRIUM** MOLLY

In this appendix we prove the assertion that *Equilibrium** completely eliminates components of the slow forces in the directions of the fast forces. This is important because it means that, at least in the linear case, *Equilibrium** is a true multiscale integrator: one is able to choose the time step for one component of the forces independently of other forces. The experimental limitations of the method are thus attributed to the fact that one is only approximating this filter in practical implementations of MOLLY, by only including part of the fast forces (bonded forces) in the mollification or averaging.

We assume that U^{fast} and U^{slow} are given by

$$U^{\text{fast}} = \frac{1}{2}(x - x_0)^T A^{\text{fast}}(x - x_0), \quad (\text{A1})$$

$$U^{\text{slow}} = \frac{1}{2}x^T A^{\text{slow}}x + b^T x + \gamma, \quad (\text{A2})$$

where $U_{xx}^{\text{fast}} = A^{\text{fast}}$ is symmetric semi-positive definite and $A^{\text{fast}} + A^{\text{slow}}$ is *symmetric positive definite (s.p.d.)*.

Note that if U^{fast} includes a linear term $a^{\text{fast}}x$ more general than $x_0 A^{\text{fast}}x$, the limit $\tau \rightarrow \infty$ of Backward Euler may not be defined, and *Equilibrium** would not either. The requirement on $A^{\text{fast}} + A^{\text{slow}}$ ensures that the analytical solution is bounded. Thus, our model problem is the most general suitable linear problem.

Next, we derive *Equilibrium** as the infinite τ limit of the Backward Euler method, which is given by

$$a = x - \tau^2 M^{-1} A^{\text{fast}}(a - x_0), \quad (\text{A3})$$

where $a = \mathcal{A}(x)$.

We require that the method be stable in the sense that the energy is bounded. The following theorem establishes that the solution and hence the energy is bounded.

Theorem 1 *Let the general linear problem $U^{\text{fast}} = \frac{1}{2}(x - x_0)^T (A^{\text{fast}})(x - x_0)$, $U^{\text{slow}} = \frac{1}{2}x^T A^{\text{slow}}x + b^T x + \gamma$, with A^{fast} symmetric semi-positive definite, and $A^{\text{fast}} + A^{\text{slow}}$ s.p.d, be discretized using the Equilibrium MOLLY method. This numerical integrator is stable (the solution is bounded) if $\Delta t \rho(M^{-1/2} A^{\text{slow}} M^{-1/2})^{1/2} < 2$.*

Proof.

After applying a symplectic transformation of variables to Eq. A3 we get

$$\tilde{a} = (I + \Delta t^2 \Omega^2)^{-1} \tilde{x} + \tilde{x}_0. \quad (\text{A4})$$

where Ω^2 is semi-positive definite.

If we assume that the eigenvalues of Ω^2 are in non-increasing order, then we can rewrite this matrix as $\Omega^2 = \begin{bmatrix} \hat{\Omega}^2 & 0 \\ 0 & 0 \end{bmatrix}$

where the elements of $\hat{\Omega}$ are positive. Thus, in the limit $\tau \rightarrow \infty$ Eq. A4 becomes

$$\tilde{a} = \Phi \tilde{x} + \tilde{x}_0. \quad (\text{A5})$$

where

$$\Phi = \begin{bmatrix} 0 & \\ & \hat{I} \end{bmatrix}. \quad (\text{A6})$$

At this point we will drop the tildes from the transformed variables. The discretization of the problem becomes **half a mollified kick**:

$$p^{n-1+1/2} = p^{n-1} - \frac{\Delta t}{2} \Phi L(\Phi x^{n-1} + x_0) - \frac{\Delta t}{2} \Phi b. \quad (\text{A7})$$

a vibration:

$$\text{Propagate } p^{n-1+1/2}, x^{n-1} \text{ by solving} \quad (\text{A8})$$

$$\begin{aligned} \frac{d}{dt} x &= p, \quad \frac{d}{dt} p = -\Omega^2 x \\ \text{to get } p^{n-1/2}, x^n. \end{aligned}$$

half a mollified kick:

$$p^n = p^{n-1/2} - \frac{\Delta t}{2} \Phi L(\Phi x^n + x_0) - \frac{\Delta t}{2} \Phi b. \quad (\text{A9})$$

Now, let $y^n = \begin{bmatrix} (x^n)^T & (p^n)^T \end{bmatrix}^T$. The numerical solution is given by $y^{n+1} = E y^n + e$, where E is a matrix and e is a vector given by

$$E = \begin{bmatrix} I & 0 \\ -\frac{\Delta t}{2} \Phi L \Phi & I \end{bmatrix} \begin{bmatrix} \cos(\Omega \Delta t) & \Omega^{-1} \sin(\Omega \Delta t) \\ -\Omega \sin(\Omega \Delta t) & \cos(\Omega \Delta t) \end{bmatrix} \begin{bmatrix} I & 0 \\ -\frac{\Delta t}{2} \Phi L \Phi & I \end{bmatrix}, \quad (\text{A10})$$

and

$$e = \begin{bmatrix} -\frac{\Delta t}{2} \Omega^{-1} \sin(\Omega \Delta t) (\Phi L x_0 + \Phi b) \\ -\frac{\Delta t}{2} (\cos(\Omega \Delta t) + I) (\Phi L x_0 + \Phi b) \end{bmatrix}. \quad (\text{A11})$$

Stability depends on the eigenvalues of E . To prove that the solution is bounded, we require that E be power bounded, which is the case if $\rho(E) \leq 1$. We also require that $(I + E + \dots + E^n)e$ be bounded itself. The proof proceeds in two steps: First, the power boundedness of E is proven; Second, it is shown that $(I + E + \dots + E^n)e$ is bounded.

There are two key observations in the remainder of this proof:

1. The separation of the solution into fast and slow parts produces two decoupled propagator matrices E for the fast and slow parts .
2. These matrices are rotations in phase space; if the stability condition obtained on the slow part is satisfied, then the solution is bounded. This is so because the vector e becomes zero for values of E which would make the solution unbounded.

The development of the above points is skipped for brevity. The reader is referred to Ref. 12, pp. 50-53.

APPENDIX B: GENERATION OF RANDOM VARIABLES FOR THE LANGEVIN IMPULSE INTEGRATOR

The procedure for generating the random variables for Langevin impulse, given in Appendix B of Ref. 19, is summarized here for reference. To integrate

$$I(f) = \int_0^T f(t) dW(t) \quad (\text{B1})$$

one can use the following facts:

- $I(f)$ is a Gaussian random variable,
- $E[I(f)] = 0$,
- $E[I(f)^2] = \int_0^T f(t)^2 dt$,
- $E[I(f)I(g)] = \int_0^T f(t)g(t)dt$.

Thus one can obtain $\int_0^T f(t) dW(t)$ from $(\int_0^T f(t)^2 dt)^{1/2} Z$, where Z is a Gaussian random number of mean 0 and variance 1. To generate other integrals $\int_0^T g(t) dW(t)$ we need to take the covariance of these random variables into account. Jointly Gaussian random variables Y_1, Y_2, \dots, Y_k with mean vector μ and covariance matrix C can be generated by the following formula

$$\vec{Y} = C_{1/2} \vec{Z} + \mu \quad (\text{B2})$$

where \vec{Z} is a vector of independent standard Gaussian random numbers of mean 0 and variance 1 and $C_{1/2}$ is a Cholesky factor satisfying $C_{1/2} C_{1/2}^T = C$. For our integrator the elements of C are the variances

$$c_{11} = \int_{t^n}^{t^{n+1}} (\exp(-\gamma(t^{n+1} - t)))^2 dt, \quad c_{22} = \int_{t^n}^{t^{n+1}} (1 - \exp(-\gamma(t^{n+1} - t)))^2 dt \quad (\text{B3})$$

and the covariance

$$c_{12} = c_{21} = \int_{t^n}^{t^{n+1}} \exp(-\gamma(t^{n+1} - t)) (1 - \exp(-\gamma(t^{n+1} - t))) dt. \quad (\text{B4})$$

We choose $[R_1^{n+1}, R_2^{n+1}]^T = C_{1/2} [Z_1^{n+1}, Z_2^{n+1}]^T$ as in Eq. (B2).

Given next are the analytical values for the integrals in Eqs. (B3) and (B4):

$$c_{11} = \frac{1}{2\gamma} (1 - \exp(-2\gamma\Delta t)), \quad (\text{B5})$$

$$c_{22} = \Delta t - \frac{2}{\gamma} (1 - \exp(-\gamma\Delta t)) + \frac{1}{2\gamma} (1 - \exp(-2\gamma\Delta t)), \quad (\text{B6})$$

$$c_{12} = c_{21} = \frac{1}{\gamma} (1 - \exp(-\gamma\Delta t)) - \frac{1}{2\gamma} (1 - \exp(-2\gamma\Delta t)). \quad (\text{B7})$$

The Cholesky factor for the 2 by 2 covariance matrix is

$$C_{1/2} = \begin{bmatrix} \sqrt{c_{11}} & 0 \\ \frac{c_{21}}{\sqrt{c_{11}}} & \sqrt{c_{22} - \frac{c_{21}^2}{c_{11}}} \end{bmatrix}.$$

Let $\tau_1 = \frac{1}{\gamma} (1 - \exp(-\gamma\Delta t))$, and $\tau_2 = \frac{1}{2\gamma} (1 - \exp(-2\gamma\Delta t))$. Then the random numbers needed for the algorithm are

$$\begin{bmatrix} R_1^{n+1} \\ R_2^{n+1} \end{bmatrix} = \begin{bmatrix} \sqrt{\tau_2} & 0 \\ \frac{\tau_1 - \tau_2}{\sqrt{\tau_2}} & \sqrt{\Delta t - \frac{\tau_1^2}{\tau_2}} \end{bmatrix} \begin{bmatrix} Z_1^{n+1} \\ Z_2^{n+1} \end{bmatrix}. \quad (\text{B8})$$

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TABLE I. **Higher accuracy results** for Langevin dynamics methods on a 10 Å radius sphere of flexible TIP3P water: maximum time step Δt for error of 0 – 0.4% in the energy.

Damping γ (ps ⁻¹)	LM	BBK-M Δt (fs)	BBK-I	LN
0.2	10	8	N/A	N/A
0.5	12	11	N/A	N/A
1	15	11	5	N/A
5	15	9	7	N/A
10	15	16	7	6
20	15	16	8	10
50	20	17	8	50
100	25	6	4	N/A

TABLE II. **Lower accuracy results** for Langevin dynamics methods on a 10 Å radius sphere of flexible TIP3P water: maximum time step Δt for error of 0.4 – 5% in the energy.

Damping γ (ps ⁻¹)	LM	BBK-M Δt (fs)	BBK-I	LN
0.2	14	12	N/A	N/A
0.5	16	15	N/A	N/A
1	16	16	N/A	N/A
5	17	18	N/A	7
10	17	18	11	15
20	25	25	17	21
50	35	18	16	50
100	40	7	N/A	50

TABLE III. **Self-diffusion coefficients** for Langevin dynamics simulations of 141 flexible TIP3P water molecules. It was computed using Einstein's relation for 20 ps chunks of 250 ps trajectories, averaging over all time origins and oxygen. The error bar is given by one standard deviation. The row for a friction coefficient $\gamma = 0.0$ corresponds to leapfrog (for the BBK-M column) and *Equilibrium** (for the LM column). Note the pronounced effect of damping in the diffusion coefficient for values of γ greater than 0.2.

Damping γ (ps ⁻¹)	BBK-M		LM	
	Δt (fs)	$D(10^{-5} \text{ cm}^2/\text{s})$	Δt (fs)	$D(10^{-5} \text{ cm}^2/\text{s})$
0.0	1	5.2 ± 0.1	1	5.2 ± 0.1
0.2	6	5.2 ± 0.1	6	5.0 ± 0.3
	8	5.1 ± 0.1	8	5.0 ± 0.3
	10	4.9 ± 0.2	10	5.2 ± 0.3
	12	4.9 ± 0.1	14	5.1 ± 0.2
	1	4.0 ± 0.2	1	4.8 ± 0.4
0.5	12	3.6 ± 0.1	12	3.6 ± 0.2
	15	3.4 ± 0.1	16	3.7 ± 0.1
	7	3.2 ± 0.2	1	2.7 ± 0.1
1.0	17	3.1 ± 0.1	16	2.9 ± 0.2
	1	1.09 ± 0.01	1	1.07 ± 0.04
10.0	16	1.08 ± 0.01	16	1.04 ± 0.01

TABLE IV. **Self-diffusion coefficients** for Langevin dynamics simulations of a protein-DNA interaction of the estrogen receptor ER and part of the DNA of an estrogen response element ERE in a 35 Å radius sphere of water with 17527 atoms. It was computed using Einstein's relation for 10 ps chunks of 20 ps trajectories, averaging over all time origins and all atoms. The error bar is given by one standard deviation. The row for a friction coefficient $\gamma = 0.0$ corresponds to the Verlet-I/r-RESPA method.

Damping $\gamma(\text{ps}^{-1})$	$\Delta t(\text{fs})$	BBK-M $D(10^{-5} \text{ cm}^2/\text{s})$
0.0	4	1.2 ± 0.1
0.2	8	1.1 ± 0.3
	10	1.2 ± 0.2

TABLE V. **CPU times** for NAMD 2.1 on the estrogen receptor ER/ERE and water system with 17527 atoms for 1008 fs. The number of processors is denoted by p . The machine was an HP K-box running HPUX 11.

Method	$\Delta t, \delta t$ (fs)	$p=1$	2 (seconds)	4
Verlet-I/r-RESPA	4,1	23783.8	14052.9	7425.3
<i>Equilibrium</i>	6,1	17929.4	10437.2	5644.0
BBK-M	16,1	8684.3	4949.3	2704.4
BBK-M	16,2	7305.2	4232.3	2266.7

TABLE VI. **Method speedups** for NAMD 2.1 on the estrogen receptor ER/ERE and water system with 17527 atoms for 1008 fs. The number of processors is denoted by p . The machine was an HP K-box running HPUX 11.

Method	$\Delta t, \delta t$ (fs)	Method speedup
Verlet-I/r-RESPA	4,1	1
<i>Equilibrium</i>	6,1	1.3
BBK-M	16,1	2.8
BBK-M	16,2	3.3

FIG. 1. System of three charged particles and one spring

FIG. 2. Maximum achievable Δt for 4 MTS Langevin dynamics integrators. The accuracy criterion was that the error in the average energy was no more than 3% with respect to the average obtained with leapfrog and $\Delta t = 1$ fs.